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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/054,365	11/12/2001	Carol W. Readhead	18810-81606	9234

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EXAMINER	
SINGH, ANOOP KUMAR	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/054,365	READHEAD ET AL.	
	Examiner	Art Unit	
	ANOOP SINGH	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *183-186, 189-196, 199-205, 208-210 and 211-257* is/are pending in the application.

4a) Of the above claim(s) *212-257* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *183-186,189-196,199-205 and 208-211* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendment to the claims filed May 30, 2008 have been received and entered. Applicants have amended claims 183-184, 186, 189-194, 196, 199-205, 208-211, while claims 1-182, 187-188, 197-198, 206, 207 have been canceled.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 05/30/2008 has been entered.

Election/Restrictions

Applicant's election of Group I drawn to non-human transgenic vertebrate was acknowledged. Claims 183-186, 189-196, 199-205, 208-210 and 211 were drawn to elected subject matter and currently under examination as they are drawn to a non-human transgenic vertebrate.

Claims 212-257 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 1/9/2004.

Claims 183-186, 189-196, 199-205, 208-210 and 211 are under examination.

Priority

It is noted that instant application is a DIV of 09/191,920 filed 11/13/1998 now US Patent 6,316,692 which claims benefit of 60/065,825 filed on 11/14/1997. Upon review of the disclosure of the prior-filed application, '825 fails to provide

explicit or implicit descriptive support for a nonhuman mammal whose germ cell comprises lentiviral vector as recited in claims 183-186, 189-196, 199-205, 208-210 and 211 of this application. In case, if applicants have evidence to support otherwise, applicants are invited to indicate page and line number for the written support in '825 as recited in claims 183-186, 189-196, 199-205, 208-210 and 211. Therefore, the effective filing date for instant claims 183-186, 189-196, 199-205, 208-210 and 211 is 11/13/19998 as stated in previous office action.

Withdrawn-Claim Rejections - 35 USC § 112

Claims 183-186, 189-196, 199-205, 208-210 and 211 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. Applicants' amendments and arguments filed May 30, 2008 have been fully considered are persuasive. Applicants' amendments to the claim now specifically recite that the injected animals are host or founder animal and only the germ cell is transgenic. Therefore, rejection pertaining to this issue is withdrawn. Additionally, Examiner would also agree that claimed transgenic non human mammal could be used in various routinely used method including *in vitro* fertilization, animal cloning, and biochemical. Therefore, rejection of claims 183-186, 189-196, 199-205, 208-210 and 211 is hereby withdrawn. However, upon further consideration claims 193-196, 199-205, 208-210 and 211 are subject to new rejection under 35 U.S.C. 112 set forth below.

New Grounds of Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 193-196, 199-205, 208-210 and 211 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for
(i) a non-human host mammal, comprising transgenic germ cells carrying in their genomes a lentiviral vector comprising at least one xenogeneic polynucleotide, so that any progeny animals are transgenic, said non-human host mammal having received an injection in its testis of male germ cells comprising a lentiviral vector comprising at least one xenogeneic polynucleotide encoding a desired product and at least one polynucleotide encoding a genetic selection marker, wherein said xenogeneic polynucleotide is xenogeneic to both said vector and said host, said male germ cells comprising the polynucleotide being isolated or selected from an allogeneic donor male non-human mammal with the aid of the selection marker, and
(ii) a non-human host mammal, or its transgenic progeny, comprising a germ cell carrying in its genome a lentiviral vector comprising at least one xenogeneic polynucleotide, wherein said xenogeneic polynucleotide is xenogeneic to both said vector and said host, said lentiviral vector comprising the polynucleotide having been incorporated into the genome of said germ cell through: (a) obtaining a male germ cell from a allogeneic non human mammal; (b) transfecting the germ cell *in vitro* with a lentiviral vector comprising at least one xenogeneic polynucleotide, wherein said xenogeneic polynucleotide is xenogeneic to both said vector and said host encoding a desired product, and allowing the lentiviral vector and the xenogeneic polynucleotide encoding a desired product to be taken up by, and released into the germ cell, and then injecting cells into testis of the nonhuman host mammal,

does not reasonably provide enablement for transplanting germ cell from one species of mammal to the testis of different species of mammal or interspecies xenogenic transplant to produce transgenic nonhuman mammal or a progeny thereof. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ 1400, 2d at 1404. Such factors are: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the art; (4) The level of one of ordinary skill in the art; (5) The level of predictability in the art; (6) The amount of direction and guidance provided by Applicant; (7) The existence of working examples; and (8) The quantity of experimentation needed to make and/or use the invention.

The office has analyzed the specification in direct accordance to the factors outlines in *In re Wands*. MPEP 2164.04 states: "[W]hile the analysis and conclusion of a lack of enablement are based on factors discussed in MPEP 2164.01(a) and the evidence as whole, it is not necessary to discuss each factor in written enablement rejection." These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled.

Claims 193-196, 199-205, 208-210 and 211 are broad in scope. The following paragraph will outline the full scope of the claims. The claims are directed to a non human mammal comprising transgenic germ cell carrying in its genome a lentiviral vector, wherein said male germ cell comprising the polynucleotide being isolated or selected from any species of donor male non human mammal. The claims are further directed to a non human host mammal or its progeny comprising a germ cell carrying a lentiviral vector comprising xenogenic polynucleotide sequence by obtaining the male germ cell from any species of nonhuman vertebrate and then transfecting the germ cell *in vitro* to produce the non human host mammal. Thus,

breadth of instant claims read on transplanting germ cells from one species to another to produce a nonhuman host mammal comprising transgenic germ cell or its progeny.

The specification teaches methods for producing genetically modified genome of an animal, by addition, modification, or subtraction of genetic material, often resulting in phenotypic changes (see page 5 of the specificaiton). The specification further asserts that generation of transgenic animals expressing agents that are of therapeutic benefit for use in human and veterinary medicine including the production of pharmaceuticals in domestic cows' milk, such as factors which enhance blood clotting for patients with types of hemophilia, or hormonal agents such as insulin and other peptide hormones (see page 15 and 16 of the specification). While the specification has contemplated that methods of the invention may be used to create any nonhuman transgenic vertebrate of any species, the guidance provided by the specification correlated only to transfection of the testis of a male mouse to generate transgenic mouse comprising lentiviral-comprising GFP (examples 3-9). It is unpredictable if the implantation of a genetically modified male germ cell from one species of nonhuman mammal to another species involving interspecies xenogenic transplantation using more distantly related species would be successful. The specification provides guidance for a method of producing a transgenic mouse by injecting a lentiviral vector comprising a xenogenic polynucleotide into the testis of a male mouse. The specification fails to provide enabling disclosure for the xenogenic interspecies transplantation to produce non human mammal comprising transgenic germ cells.

The claims embrace any nonhuman host mammal or its transgenic progeny, comprising a germ cell carrying in its genome a lentiviral vector comprising at least one xenogeneic polynucleotide by obtaining a male germ cell from any species of a non human mammal and transfecting the germ cell *in vitro* with a lentiviral vector. It is noted that the method steps of claim 203 is inconsistent as it recites obtaining

a male germ cell from a nonhuman vertebrate which is broader then nonhuman mammal. It is noted that genetically modifying male primordial germ cell from a bony fish or amphibian and subsequent implantation of germ cells into the testis of nonhuman mammal would not be predictable to produce genetically modified nonhuman host mammal. The specification has exemplified administering genetic material (GFP) into the testis of a mouse and reverse transcriptase PCR analysis of tissues obtained from the testis show presence of GFP in the injected testes (see example 7-8). The specification also describes the *in vitro* transfection of testicular cells isolated from the testis of a mouse that is then injected into the testis of the mouse via the *vasa efferentia*. It is noted that only two out of three males survived that were bred with normal females resulting in progeny of nonhuman mammal. The specification fails to provide any guidance with respect to the integration of the transgene in the litters (see example 10). The claims as recited are clearly interpreted to read on interspecies xenotransplantation of genetically modified germ cells. One of skill could not rely on the state of the interspecies xenotransplantation art for guidance because the state of the xenotransplantation art is unpredictable with respect to implantation of germ cells into the testes across different animal species. Griswold et al (Journal of Andrology, 2001, 22, 713-717) taught that mixture of germ cells from either mouse or rat testes were successfully transplanted by microinjection into a germ cell-depleted recipient mouse testis (see page 713, col. 1, para. 1). Ogawa et al (Biol. Reprod. ,1999, ;60(2):515-21) disclose injecting hamster germ cells into immunocompromised murine testes to successfully colonized the tubules and completed spermatogenesis (abstract). However, abnormal developing germ cells and abnormal sperm were found in the seminiferous tubules and the epididymis, respectively (see page 519, col. 1, para. 1 ad figure 2). This is further supported by Dobrinski et al (Mol Reprod Dev. 2000; 57(3):270-9 and Biol Reprod. 1999; 61:1331-1339) who discloses that fresh and cryopreserved germ cells could colonize the mouse testis but do not differentiate

beyond the stage of spermatogonial expansion. It is disclosed that no cells from either dog or rabbit progressed into meiotic stages and no mature sperm were observed. Similar results were reported for the larger domestic species (See Dobrinski 2000). It is noted that Dobrinski (Mol Reprod Dev. 2000 Nov;57(3):270-9) observed donor cells in most recipient mouse testes with some species differences in the pattern and extent of colonization, but in each case, no advanced germ cells were formed (see abstract and entire document). In any event, the guidance provided by the specification failed to correlate to the donor-host combinations embraced by the claims, particularly in light of the unpredictability of the interspecies xenotransplantation of germ cell art as set forth by the references above. The lack of guidance in the specification would force the skilled practitioner to guess and try interspecies xenotransplantation of germ cell. Such guessing would require extensive and undue experimentation. Applicant should note that "case law requires that the disclosure of an application shall inform those skilled in the art how to use applicants' alleged discovery, not to find out how to use it for themselves." *In re Gardner* 166 USPQ 138 (CCPA) 1970. Given the lack of guidance provided by the specification with respect to donor-host compatibility of xenotransplantation of germ cells it would have required undue experimentation to make and use the invention as claimed for producing transgenic nonhuman mammal without a reasonable expectation of success.

In conclusion, in view of breadth of the claims and absence of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by applicant is not enabled commensurate with full scope of the claimed inventions. The specification and prior art do not teach method of interspecies xenotransplantation of male germ cells to produce transgenic nonhuman mammal. An artisan of skill would have to perform undue experimentation to make and use the invention because the art of interspecies xenotransplantation of germ cells to produce transgenic animal or its progeny was

unpredictable at the time of filing of this application as supported by the observations in the art record.

Withdrawn-Claim Rejections- 35 USC § 102

Claims 183-184, 189-194, 199-202 were rejected under 35 U.S.C. 102(e) as being anticipated by Bryant et al (US Patent 6156952 dated 12/5/2000, effective filing date 4/19/1998). Applicants have amended base claims 183 and 193 to specifically recite that the injected animals are host or founder animal and only the germ cell is transgenic. The rejection is hereby withdrawn as Bryant et al teach conventional transgenic nonhuman mammal comprising transgene in somatic as well as germ cells. Therefore, method of Bryant would result in distinct product compared to one resulting from method of claim 183 or 193.

Claims 183-186, 189-190, 196, 199-200, 203-205, 208-210 and 211 were rejected under 35 U.S.C. 102(b) as being anticipated by Leonard et al (AIDS Res Hum Retroviruses. 1989; 5(4): 421-30). Applicants have amended claims to overcome the rejection of record for the reason discussed above. Additionally, Leonard et al do not teach transgenic non human mammal carrying lentiviral vector integrated in the genome of the germ cells.

Maintained -Claim Rejections- 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 185-186, 195-196, 203-205, 208-210 and 211 remain rejected under 35 U.S.C. 102(e) as being anticipated by Bryant et al (US Patent 6156952 dated 12/5/2000, effective filing date 4/19/1998, art of record).

Applicants arguments filed May 30, 2008 have been fully considered but are not persuasive. Applicants argue that Bryant et al are generating transgenic mice by using the classic method of injection of the gene construct into the fertilized egg as opposed to the transduction of male germ cells as required by the claims of the present invention. Applicants assert that the method of Bryant et al is different from that of the present invention and the immediate product of the process is also different, as the product of the current invention is a transduced male germ cell (see applicants' argument page 21, para. 1).

As an initial matter it is noted that rejection of claims that were directed to a nonhuman mammal carrying lentiviral vector only in germ cells have been withdrawn. However, rejections to claims directed to a progeny of nonhuman transgenic mammal are maintained for the reasons of record. Instant claims are product by process claims and require xenogeneic polynucleotide in the germ as well as somatic cells of the resulting transgenic progeny. Claims 203-211 have been included in the rejection as they all read on transgenic progeny.

Applicants' arguments of classic method of injection of the gene construct into the fertilized egg as opposed to transduction of male germ cells is not persuasive because a progeny nonhuman mammal resulting from the claimed methods would carry polynucleotide sequence in germ as well as somatic cell. Bryant et al teach transgenic non-human animal whose genome comprises lentiviral and at least one additional transgene including human CD4 receptor gene or a gene involved in a disease (see col. 4, lines 8-20, 30-40 and 58-65). In addition, Bryant et al also disclose a method of producing the transgenic nonhuman animal described identification and quantitation of transgenes in the founder animals and their progeny (see col. 14 and 15). Brynat et al contemplate transgenic animal of the

invention includes mouse, rat, rabbit, pigs, baboons and monkeys (see col. 10, lines 48-52). The progeny transgenic nonhuman animal disclosed by Bryant et al and those embraced by the instant claims appear to be structurally same. Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the *prima facie* case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best*, 562 F.2d at 1255, 195 USPQ at 433. Furthermore, MPEP § 2113 states, "Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process."

Accordingly, Bryant et al anticipates claims 185-186, 195-196, 203-205, 208-210 and 211.

New-Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 183-186, 189-196, 199-205, 208-210 and 211 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brinster et al (US Patent 5,858,354, dated 1/12/1999, filed on 11/21/1994, art of record) and Naldini et al., (Science, 1996, 272: 263-267, IDS).

The claims are directed to a non human mammal comprising transgenic germ cell and a progeny thereof. Claims are also directed to a nonhuman mammal comprising transgenic germ cell by obtaining a donor or native male germ cell from a non-human mammal and transfecting the germ cell in vitro with at least one polynucleotide encoding a gene product and allowing the polynucleotide to be taken up and released into the germ cell.

Claim interpretation: Instant claims are product by process claims (see MPEP § 2113). Claim 183 is interpreted to embrace a nonhuman mammal comprising genetically modified male germ cells. It is noted that while base claim only requires germ cells be transduced with the polynucleotide sequence, however, resulting progeny set forth in claims 185 would contain transgene in somatic as well as germ cell. Claim 193 is interpreted to embrace a non human host mammal comprising transgenic germ cell, wherein male germ cell comprising the polynucleotide being isolated or selected from a donor male non human mammal. Thus, breadth of these claims embraces genetically modifying germ cell of a donor male and then transplanting germ cell into host male animal. Claim 203 is interpreted to embrace a nonhuman host mammal that is obtained by obtaining germ cell from any nonhuman mammal and then transfecting the germ cell *in vitro* with lentiviral vector comprising polynucleotide such that desired product that is taken up and released into the germ cell. The *in vitro* transfected germ cell upon transplantation into the host mammal is interpreted as native to the host mammal. It is noted that method steps recited in the claims do not require *in vitro* transfected germ cell to be same as native germ cell. Therefore, a male germ cell

from non human mammal that is transfected *in vitro* with the vector upon transplantation into the host mammal is interpreted as native germ cell.

Regarding a non human mammal comprising transgenic germ cell, Brinster et al. teach introduction of the transgene construct to a sperm that could be introduced to the seminiferous tubules of a host male animal (Brinster et al., col., 13, lines 14-17). Brinster et al. also teach that male germ cells are cultured at around or below the body temperature (32^0C) because of their sensitivity to high temperatures (Brinster et al., col. 6, lines 30-32) and same could be used for transfection. Practicing the methods claimed by Brinster *et al.* result in a transgenic animal comprising germ cells that have been genetically modified with a transgene meeting the limitation of base claim 183, 193 and 203.

Brinster et al. teach that the heterologous DNA sequence can be transferred into the germ or other primitive cells by a viral vector, such as a retroviral vector or an adenoviral vector (Brinster et al., col., 7, line 66 to col. 8, line 9). Brinster et al. teach a method of *in vitro* transfection primitive germ cells (Brinster et al., col. 5-7, especially, col. 6, line 1, 30, col. 7, lines 36-45) with a heterologous DNA sequence encoding a gene of interest (Brinster et al., col. 8, lines 33-49). Brinster et al. further teach that the DNA sequence may be obtained from a source of the same species or from different species (Brinster et al., col. 8, lines 50-55). Brinster et al. further teach that such methods may be applicable to any species of animals, in which the male has testes including mice, rat, swine and other farm animals (Brinster et al., col. 10, and lines 27-43). It is also disclosed that the primitive cells may also be native cells possessing naturally or artificially induced mutation (see col. 7, line 42). Brinster et al. further teach that cell comprising the transgene construct can be tracked by including a nucleic acid sequence encoding a genetic marker (e.g. lacZ) operably linked to a sperm-specific promoter (Brinster et al., col., 11, line 58 to col. 12, line 19).

With respect to claims drawn to progeny non human mammal, Brinster et al. teach that progeny mice comprising the transgene were obtained following treatment of primitive cells with a transgene (Brinster et al., col., 18, lines 57-65, col., 19, lines 4-6).

While Brinster et al. teach that a wide variety of viral vectors that could be used to produce a nonhuman mammal comprising transgenic germ cell or a progeny thereof, they do not specifically teach use of lentiviral vectors.

However prior to filing of instant application, lentiviral vectors were known to be more efficient than other vectors in transducing cells and provided a more sustained level of expression. Naldini et al. cure the deficiency of Brinster et al by teaching lentiviral vectors that could be used to deliver gene of interest to non dividing cell more efficiently as compared to other viral vectors (see abstract and entire article).

At the time of filing of this application it would have been obvious to one of ordinary skill in the art to modify the method of producing a non human mammal comprising transgenic germ cell or a progeny thereof disclosed by Brinster et al. by substituting adeno or retroviral vector with equivalent lentiviral vector with a reasonable expectation of success of achieving predictable result. One of ordinary skill in the art would be motivated to substitute one viral vector as disclosed by Brinster with another such as lentiviral vector as disclosed by Naldini as a matter of design choice to improve transfection efficiency. Given that Brinster et al. provide guidance that a wide variety of viral vectors can be used for delivery of a gene of interest, using another vector, i.e., a lentiviral vector, is a matter of design choice and an artisan would have been as likely to use a lentiviral vector as any other viral vector in a method of introducing a transgene to a germ cell to produce nonhuman mammal comprising transgenic germ cell and transgenic progeny therefrom. One of skill in the art would have had a reasonable expectation of success in combining the teachings of Brinster with those of Naldini because it was routine in the art at the

time of filing to substitute the one viral vector disclosed by Brinster with another to improve transduction efficiency to produce transgenic nonhuman mammal.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Conclusion

No Claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANOOP SINGH whose telephone number is (571)272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Anoop Singh/
Examiner, Art Unit 1632